Managing Acute Uncomplicated Cystitis in Women in the Era of Antibiotic Resistance

Highlights of a Scientific Roundtable

The third in a series of educational newsletters

PRESENTED BY

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Please direct all correspondence to:

IMED Communications
Department 165
518 Route 513
PO Box 458
Califon, NJ 07830

PROGRAM CHAIR

Lindsay E. Nicolle, MD, FRCPC
Professor
Department of Internal Medicine
University of Manitoba
Winnipeg, MB, Canada

CME/CE PLANNING COMMITTEE

Thomas M. Hooton, MD
Professor of Medicine
Department of Medicine
University of Washington School of Medicine
Seattle, WA

Wanda K. Jones, DrPH
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Office on Women's Health
Department of Health and Human Services
Washington, DC

Anne Moore, RNC, MSN, CNP
Professor of Nursing
Women's Health Nurse Practitioner
Vanderbilt University
Nashville, TN

Lindsay E. Nicolle, MD, FRCPC
Professor
Department of Internal Medicine
University of Manitoba
Winnipeg, MB, Canada

Sandy Pomerinke
Program Coordinator
University of Washington School of Medicine
Seattle, WA

FACULTY

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Assistant Professor
Department of Surgery
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Department of Medicine
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Seattle, WA

Thomas M. Hooton, MD
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Department of Medicine
University of Washington School of Medicine
Seattle, WA

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VA Puget Sound Urology
Seattle, WA

Mark G. Martens, MD, FACOG
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Tulsa, OK

Anne Moore, RNC, MSN, CNP
Professor of Nursing
Women's Health Nurse Practitioner
Vanderbilt University
Nashville, TN

Lindsay E. Nicolle, MD, FRCPC
Professor
Department of Internal Medicine
University of Manitoba
Winnipeg, MB, Canada

Allan Ronald, MD, FRCPC
Emeritus Professor
University of Manitoba
Faculty of Medicine
St. Boniface Hospital
Winnipeg, MB, Canada

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Mayo Clinic
Rochester, MN

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Department of Medicine
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School of Medicine
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Product	Off-Label Use
All UTI therapies	Prophylaxis

TARGET AUDIENCE

Urologists, obstetricians/gynecologists, primary care physicians (general practitioners, family practitioners, internal medicine physicians), nurse practitioners and other healthcare professionals who care for patients with acute uncomplicated cystitis.

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MANAGING ACUTE UNCOMPLICATED CYSTITIS IN WOMEN IN THE ERA OF ANTIBIOTIC RESISTANCE

INTRODUCTION

Acute uncomplicated cystitis (AUC) is a common and usually benign urinary tract infection (UTI) that affects women of all ages. The diagnosis and management of UTIs is generally straightforward; the evolution of antimicrobial resistance, however, necessitates continuing reassessment of standard empiric therapy.

This is the third in a series of continuing medical education newsletters based, in part, on discussions from an August 2002 roundtable presented by the Office on Women's Health of the U.S. Department of Health and Human Services and jointly sponsored by the University of Washington School of Medicine and IMED Communications. This newsletter highlights the impact of resistance on the management of AUC in healthy women.

When selecting an antimicrobial, the clinician also needs to consider the broader uses of the drug and the potential for promoting resistance that may compromise the drug's utility in treating other, more serious infections or diseases.

Clinicians face several challenges in managing AUC. From the perspective of the patient, treatment should be safe and effective, providing prompt resolution of symptoms with few side effects and little chance of recurrence. When selecting an antimicrobial, the clinician also needs to consider the broader uses of the drug and the potential for promoting resistance that may compromise the drug's utility in treating other, more serious infections or diseases.

Resistance of uropathogens to various agents has made treatment of AUC less straightforward than it was previously:

- The efficacy of ß-lactams, once among the mainstays of therapy for lower UTIs, has been seriously compromised. In a national survey, resistance to ampicillin and cephalothin ranged from 20% to nearly 35%, suggesting that these agents are poor choices for empiric therapy.[1]
- Resistance to trimethoprim-sulfamethoxazole (TMP/SMX), often the first-line agent in empiric treatment of AUC, has increased from 9% to 18%, approaching 30% in some US regions.[1]
- Rates of resistance to ciprofloxacin remain relatively low but are increasing gradually. The resistance of *Escherichia coli* urinary isolates in ambulatory women increased from 0.7% in 1995 to 2.5% in 2001.[2] There is concern that the widespread use of ciprofloxacin and other fluoroquinolones for the treatment of UTI may contribute to resistance in other nonurinary pathogens, such as *Streptococcus pneumoniae*, decreasing the utility of fluoroquinolones for treatment of serious infections caused by such pathogens.[3]

There are several fluoroquinolone-sparing alternatives for empiric therapy of AUC. Nitrofurantoin, in use for nearly 50 years, is indicated exclusively for the treatment of cystitis, and the prevalence of resistant *E coli* has remained low during its long history of safe and effective use. Fosfomycin has also recently been introduced for treating lower UTIs, and significant resistance has not emerged, but experience with this agent is limited to date.

LEARNING OBJECTIVES

Upon completion of this program, the participant should be able to:

- Discuss the etiology of acute cystitis
- Describe the impact of the growth of antimicrobial resistance on the management of acute cystitis
- Determine the risk factors that influence the development and recurrence of acute cystitis in at-risk populations
- Identify the benefits and disadvantages of both traditional and newer antimicrobial agents
- Review the latest pharmacologic/nonpharmacologic strategies for treatment and prevention of acute uncomplicated cystitis

Most clinicians would agree that it is unrealistic to expect patients to forego effective treatment in the interest of preventing resistance in the community; with UTI-specific agents such as nitrofurantoin and fosfomycin, both with low rates of *E coli* resistance and proven safety and efficacy, AUC can be treated optimally from both the patient and the community perspective.

UTI TERMINOLOGY

UTIs affect people of all ages, from newborns to the elderly. Clinical severity ranges from asymptomatic bacteriuria (ASB) to infections necessitating hospitalization and resulting in significant morbidity. UTIs are categorized as follows:

- *ASB*: presence of bacteria in the urine without clinical symptoms;
- *Cystitis*: infection of the bladder—usually designated as uncomplicated or complicated;
- *Pyelonephritis*: infection of the kidneys, which may be uncomplicated or complicated.

The distinction between uncomplicated and complicated UTIs has important treatment implications. In general, complicated UTIs occur in individuals with functional or structural abnormalities of the genitourinary tract.[4] A UTI is considered complicated when one or more of the following factors are present: urinary calculi, cystic renal disease, obstruction, anatomic abnormalities, neurologic bladder dysfunction, or a foreign body. Host factors may also complicate a UTI; these include pregnancy, diabetes, transplanted kidneys, prostatic involvement, and other metabolic or immunologic illnesses.[5] Complicated UTIs are associated with increased risk both for repeat infections and for therapy failure.[6]

By the age of 24 years, about 1 of every 3 women will have had at least 1 UTI necessitating antimicrobial treatment...

EPIDEMIOLOGY

UTI is the most common bacterial infection.[7] During the first 3 months of life, UTIs are about 3 times more common in males than in females. In all other age groups, UTIs are more common in females. In school-age children, significant bacteriuria is prevalent in 1.2% of girls and 0.04% of boys, a female-to-male ratio of 30 to 1. The prevalence of bacteriuria continues to increase with age in women, by about 1% per decade, and is 8% to 10% or higher in elderly community-dwelling women.[8]

The incidence of symptomatic UTIs is high among sexually active women. By the age of 24 years, about 1 of every 3 women will have had at least 1 UTI necessitating antimicrobial treatment, and 40% to 50% of all women will have at least 1 UTI during their lifetimes. In a telephone survey of 2000 American women, 10.8% of those more than 18 years of age reported having at least 1 UTI in the previous year; most of these had a history of at least 2 previous UTIs. The lifetime prevalence of UTI was 60.4%.[7,9]

The costs of UTIs are high. A survey of medical facilities in 1997 found that UTIs accounted for more than 7 million physician office and outpatient visits and about 1.25 million emergency department visits each year.[10] Direct treatment costs were estimated at $659 million in 1995, with an additional $936 million in indirect costs. When the costs of treating nosocomial UTIs, estimated at $450 million per year, are also considered, the total cost of treating UTIs in the United States exceeds $2 billion annually.[9]

Although AUC is generally a relatively benign illness with no long-term adverse medical sequelae, there are important short-term consequences. An episode results in an average of 6 days with symptoms, 2.4 days of restricted activity, 1 day of time lost from work, and 0.4 days of bed rest. From 20% to 30% of women will experience recurrent UTIs (RUTIs) within 3 to 4 months of the initial infection.[7]

RISK FACTORS

Behaviors identified as risk factors for AUC in young women include sexual intercourse, frequency of intercourse, and contraceptive method. In a large, prospective study, recent sexual intercourse, recent use of a diaphragm with spermicide, and history of RUTIs were all independent risk factors for UTI.[11]

The use of spermicide is an independent risk factor for UTI. In the previous study, use of spermicide alone significantly increased the risk of UTI ($P<.001$).[11] A case-control study in a large health maintenance organization found that the risk of UTI was 3 times higher for women exposed to spermicide-coated condoms than for sexually active women who did not use coated condoms, even after adjustment for other risk factors.[12]

Other behavioral factors reported to increase the incidence of UTIs include recent antibiotic use and having a new sexual partner.[13] On the other hand, no conclusive links have been found with a range of potential factors including wearing pantyhose, use of tampons, wiping patterns, postcoital voiding patterns, douching, and the volume of fluid intake.[14]

UTIs are more common in immediate female relatives (mothers, sisters, daughters) of patients with recurrent infection. In a study with 229 women with RUTIs and 253 controls, more than 45% of those with RUTIs reported that their mothers had UTI histories vs approximately 26% of controls.[15] This suggests a role for genetic factors in women with RUTI.

ETIOLOGY

E coli is the most important pathogen in AUC, responsible for 80% to 90% of cases. *Staphylococcus saprophyticus* is isolated from 5% to 15%, and pathogens such as *Klebsiella*, *Proteus mirabilis*, and group B streptococci are isolated in a small number.[16]

***E coli* is the most important pathogen in AUC, responsible for 80% to 90% of cases.**

The etiology of complicated UTIs is appreciably different from that of uncomplicated cystitis, with a wider range of organisms isolated (Table 1). *E coli* remains the most frequent pathogen, but other organisms are frequently isolated. Organisms that would rarely cause disease in a normal urinary tract can cause infection and illness in persons with abnormal urinary tracts.[17]

PATHOGENESIS

Uropathogenic bacteria usually originate in the gastrointestinal (GI) tract, where they colonize the colonic microflora. The proximity of the female urethra and vagina to the anus permits transfer of pathogens from the GI tract to the urinary tract. Moreover, the shortness of the female urethra (3 to 4 cm) compared with the male urethra facilitates organisms ascending into the bladder. This anatomic difference may account for much of the discrepancy in UTI incidence between men and women.[18]

The first step in the pathogenesis of most UTIs is the colonization of the vagina or the periurethral area with *E coli*. Uropathogenic strains of *E coli* have surface protein filaments, called fimbriae or pili, with adhesion molecules that interact directly with host receptors for attachment to the urethral and bladder mucosa. The adhesion filaments may mediate the internalization of bacteria into the epithelial cells, where they can replicate and evade host defenses.[17]

Spermicide use plays a large role in the pathogenesis of UTIs in some women. Spermicides probably increase the risk of UTI by altering the vaginal environment to favor colonization with uropathogens.[11,19] The majority of women who use diaphragms also use spermicide. It has been proposed that the diaphragm itself facilitates infection by depressing the urethra and bladder, leaving a pool of residual urine in which bacteria can multiply.[20]

The link between recent antibiotic use and increased UTI incidence may also be due to alterations in the vaginal flora such that colonization by uropathogens is favored.[21,22]

DIAGNOSIS OF AUC

History and Symptoms

The symptoms of AUC are caused by infection and inflammation of the bladder and the urethra. The chief symptom is dysuria; other signs and symptoms may include urinary frequency, nocturia, urgency, voiding of small volumes, incontinence, and suprapubic or pelvic pain. Some patients have hematuria or cloudy and malodorous urine.[23] Dysuria, in isolation, may be caused by other factors, such as acute urethritis due to *Chlamydia trachomatis*, *Neisseria gonorrhoea*, herpes simplex virus, vaginitis due to *Candida* spp or *Trichomonas vaginalis*. These infections generally may be differentiated by history, physical examination, and simple laboratory tests.[6,23]

TABLE 1

UNCOMPLICATED VERSUS COMPLICATED UTI PATHOGENS

Uncomplicated	Complicated
Escherichia coli (80%-85%)	*Escherichia coli*
Staphylococcus saprophyticus (5%-15%)	*Klebsiella* spp
Klebsiella spp	*Enterobacter cloacae*
Enterococcus faecalis	*Serratia marcescens*
	Proteus mirabilis
	Pseudomonas aeruginosa
	Enterococcus faecalis
	Group B streptococci
	Candida spp

Adapted from *Am J Med*, 113, Ronald A. The etiology of urinary tract infection: tradition and emerging pathogens, 14S-19S, Copyright 2002 with permission from Excerpta Medica Inc.

Patients can often distinguish between internal and external dysuria. In "internal" dysuria, the discomfort is within the bladder and urethra and begins before or with the initiation of voiding. In "external" dysuria, discomfort is localized to the perineum and does not start until after voiding has begun; external dysuria suggests vaginitis or vulvar inflammation, with irritation of the affected surfaces by the urine stream.[23]

A new sexual partner increases the likelihood of a sexually transmitted infection, presenting as vaginitis, cervicitis, or urethritis. The pattern of symptoms may be helpful to differentiate the 3 disease entities. Abrupt onset of dysuria is characteristic of bacterial cystitis caused by *E coli* or *S saprophyticus*, or of urethritis caused by *N gonorrhoea*. A more gradual onset is suggestive of urethritis caused by *Chlamydia*. Concomitant voiding symptoms (eg, frequency, urgency, voiding small volumes), in addition to dysuria, are common in cystitis, less common in urethritis, and rare in vaginitis. Gross hematuria and suprapubic pain or tenderness are rarely seen in dysuric syndromes other than AUC. Spermicide or diaphragm use by a woman presenting with dysuria supports a diagnosis of AUC, as does a history of previous UTI.[23]

Physical Examination

The physical examination is noncontributory to a diagnosis of AUC but may be useful in diagnosing or excluding other disorders. Suprapubic tenderness is present in about 10% of patients with AUC, and is fairly specific to this diagnosis. Fever and/or flank tenderness in a patient whose symptoms otherwise suggest a lower UTI may indicate renal infection. When a sexually transmitted disease is possible, pelvic examination may be indicated to identify vaginitis, cervicitis, vulvar infection, or pelvic inflammatory disease. In a postmenopausal woman, a cystocele may be evident.

Laboratory Tests

Urine culture is considered the gold standard for diagnosis of UTI. In practice, cultures are not obtained uniformly from women presenting with possible AUC because empiric therapy is initiated and often completed before the results of a urine culture are available.[24] Rapid tests that may support a diagnosis include urinalysis with direct microscopic examination of fresh or Gram-stained urine, and "dipstick" biochemical tests, such as the leukocyte esterase and the leukocyte esterase/nitrate strip.[23]

Presence of pyuria is a key indication of AUC. The excretion of more than 400,000 wbc/hr is seen in more than 95% of young women with AUC and is uncommon in the absence of infection in otherwise healthy women.[23]

A recent study attempted to identify objective criteria for confirming or ruling out a diagnosis of AUC using published trial data. Table 2, page 4 lists the symptoms and signs that increase the likelihood ratio (LR) of a diagnosis of UTI (values >1.0) and those that decrease it (values <1.0). Dysuria, frequency, hematuria, and back pain, whether self-reported or found on physical examination, significantly increase the LR of an AUC diagnosis. The symptoms that most strongly exclude UTI were found to be vaginal discharge and vaginal irritation.[25] The important diagnostic differences between cystitis, urethritis, and vaginitis are summarized in Table 3, page 4.

TABLE 2

CLINICAL PREDICTORS OF UTI

Symptom	Positive LR (95% CI)	Negative LR (95% CI)	Symptom	Positive LR (95% CI)	Negative LR (95% CI)
Self-diagnosis	4.0 (2.9-5.5)	0.0 (0.0-0.1)	Back pain	1.6 (1.2-2.1)	0.8 (0.7-0.9)
Hematuria	2.0 (1.3-2.9)	0.9 (0.9-1.0)	Dysuria	1.5 (1.2-2.0)	0.5 (0.3-0.7)
Frequency	1.8 (1.1-3.0)	0.6 (0.4-1.0)	Lower abdominal pain	1.1 (0.9-1.4)	0.9 (0.8-1.1)
Fever	1.6 (1.0-2.6)	0.9 (0.9-1.0)	Vaginal discharge	0.3 (0.1-0.9)	3.1 (1.0-9.3)
Flank pain	1.1 (0.9-1.4)	0.9 (0.8-1.1)	Vaginal irritation	0.2 (0.1-0.9)	2.7 (0.9-8.5)

LR = Likelihood ratio

CI = Confidence interval

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A diagnosis of AUC usually can be made based on the rapid tests in combination with history and physical examination. For patients whose diagnosis remains uncertain after these steps have been taken, a urine culture should be obtained. Identification of specific pathogens and their susceptibility to antimicrobials is also important in treatment for patients with suspected pyelonephritis or complicated UTI. In these situations, different pathogens may be present, and antibiotic therapy should be tailored to the individual organism and susceptibility pattern.[24]

Self-Diagnosis

A university-based study evaluated self-diagnosis and patient-initiated treatment of uncomplicated UTIs in a cohort of 172 women. Of these, 88 women self-diagnosed 172 UTIs. Patients initiated treatment after a clean-catch urine sample was obtained for culture. Uropathogens were isolated in 144 self-diagnosed episodes (84%). An additional 64 women reported episodes of mild symptoms that they did not self-diagnose as UTIs and that resolved without treatment, and 20 women had no symptomatic episodes.[26] If women with mild symptoms did not have UTIs, the positive LR for self-diagnosis is 4.0, and the negative LR is 0.0.[25] Thus, women who have previous experience with UTIs reliably recognize symptoms and can accurately self-diagnose and self-treat AUC.[26]

ANTIBIOTIC RESISTANCE AND THE MANAGEMENT OF AUC

Resistance of bacteria to antibiotics has continued to increase, with antibiotic use (much of which is inappropriate) contributing to the rise. Some common pathogens are now resistant to antibiotics previously used frequently for treatment. Some strains of *Enterococcus faecalis*, *Mycobacterium tuberculosis*, and *Pseudomonas aeruginosa* are resistant to almost every antibiotic available.[27]

The FDA recently amended its labeling requirements for empiric antibiotics, emphasizing, among other issues, the fact that using broad-spectrum antibiotics, including newer drugs, "can increase the development of resistance."

In prescribing empiric therapy for AUC, clinicians need to consider the impact of antibiotic resistance on treatment outcomes. Some current empiric treatments may select for resistant pathogens that can cause

TABLE 3

MAJOR INFECTIOUS CAUSES OF ACUTE DYSURIA IN WOMEN

Condition	Pathogen	Pyuria	Hematuria	Urine Culture	Symptoms/Signs
Cystitis	*E coli*, *S saprophyticus*, *Proteus* spp, *Klebsiella* spp	Usually	Sometimes	$\geq 10^2$-10^5	Abrupt onset, severe symptoms, multiple symptoms (dysuria, increased frequency/urgency), suprapubic/low-back pain, suprapubic tenderness on examination
Urethritis	*C trachomatis*, *N gonorrhoeae*, herpes simplex virus	Usually	Rarely	$<10^2$	Gradual onset, mild symptoms, vaginal discharge/bleeding, lower abdominal pain, cervicitis/vulvovaginal herpetic lesions on examination
Vaginitis	*Candida* spp, *T vaginalis*	Rarely	Rarely	$<10^2$	Vaginal discharge/odor, pruritus, dyspareunia, external dysuria, no increased frequency/urgency, vulvovaginitis on examination

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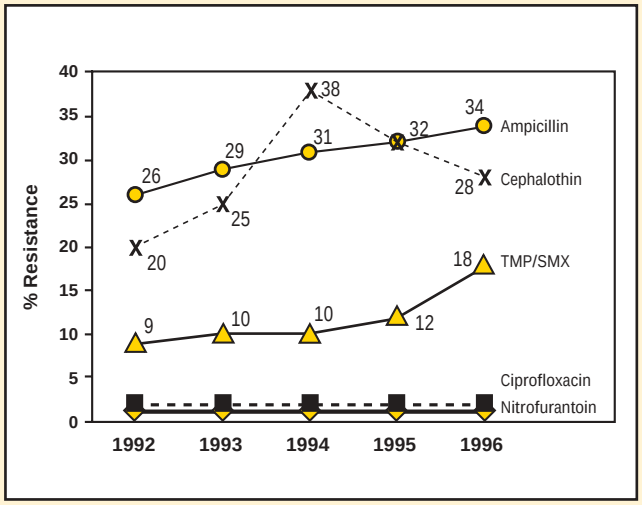
FIGURE 1

PREVALENCE OF RESISTANCE OF *E COLI* CAUSING AUC IN WOMEN[1]



recurrent UTI. The widespread empiric use of some antibiotics in treating AUC, such as the fluoroquinolones, may contribute to resistance that impairs their efficacy in treating other, more serious diseases. The FDA recently amended its labeling requirements for empiric antibiotics, emphasizing, among other issues, the fact that using broad-spectrum antibiotics, including newer drugs, "can increase the development of resistance."[28]

Increasing Prevalence of Resistant Pathogens

In 4342 urine isolates from 4082 patients with AUC, 86% were *E coli*, and 4% were *S saprophyticus*.[1] In 1992, the prevalence of resistance to ampicillin and cephalothin in *E coli* in the United States was 29% and 20%, respectively. By 1996, ampicillin resistance had reached 38%. Cephalothin resistance peaked at 37% in 1994, and declined to 28% by 1996 (Figure 1). The high levels of resistance to ß-lactams preclude the use of these drugs for empiric treatment of AUC.[1] The increasing prevalence of resistance to TMP/SMX, commonly considered a first-line agent in treating AUC, is of particular concern.[29] TMP/SMX may not be an acceptable therapeutic choice for much longer because of this increasing resistance.[1]

The increasing prevalence of resistance to TMP/SMX, commonly considered a first-line agent in treating AUC, is of particular concern.

Another study described susceptibilities of *E coli* urinary isolates from US women from 1995 to 2001 to TMP/SMX, ampicillin, ciprofloxacin, and nitrofurantoin. The percentage of isolates resistant to ampicillin was 36.4% in 1995 and 37.0% in 2001. TMP/SMX resistance increased from 14.8% to more than 16% over the 5-year period. *E coli* resistance to ciprofloxacin, initially 0.7%, tripled to 2.5%, with a gradual yearly increase. *E coli* resistance to nitrofurantoin remained below 1% throughout the period of observation.[2]

A nationwide study of 5739 urinary isolates from ambulatory women in 43 states described resistance prevalence of the 4 most common uropathogens (*E coli*, *K pneumoniae*, *P mirabilis*, and *S saprophyticus*) in 4 antibiotics commonly used to treat UTIs (TMP/SMX, cephalothin, nitrofurantoin, and ciprofloxacin).[30] Nitrofurantoin had the lowest resistance rates, 0.5% in *E coli* and 0% in *S saprophyticus*, followed by ciprofloxacin, with resistance rates of 1.7% and 0.4%, respectively; cephalothin, with 9.7% and 1.0%, respectively; and TMP/SMX, with 16.8% and 3%, respectively.[30] Resistance rates varied widely from state to state. *E coli* resistance to TMP/SMX ranged from a low of 7.4% in Pennsylvania to a high of 43.7% in Arizona. Regionally, resistance was highest in the West South-Central region (28.4%), comprising Arkansas, Louisiana, Oklahoma, and Texas, and lowest in the East South-Central region (9.2%), comprising Alabama, Kentucky, Missouri, and Tennessee (Figure 2).[30]

Regional and state variations in resistance rates are clearly relevant to treatment outcomes, so clinicians must know local rates.

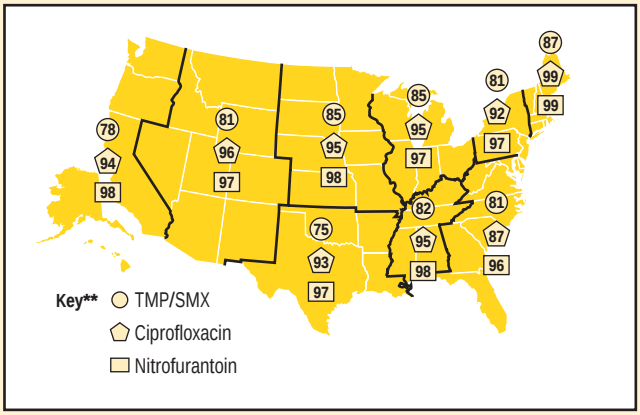
Regional and state variations in resistance rates are clearly relevant to treatment outcomes, so clinicians must know local rates. Current information showing trends in resistance rates is available from Medscape in the "UTI Zone." In addition, clinicians are encouraged to review local hospital susceptibility reports for resistance trends in their areas.

Uropathogen resistance to commonly used agents is causing concern in several other countries. Although rates of resistance to TMP/SMX in Canada and Northern Europe are similar or lower to those in the United States, higher rates have been reported in Israel (31%), Spain (32%), and Bangladesh (60%).

In Bangladesh, a resistance rate of 18% to ciprofloxacin has also been reported, and in Spain the resistance rate to norfloxacin is 13%.[26] One hospital in Spain reported an increase in fluoroquinolone use, apparently

FIGURE 2

GEOGRAPHIC VARIATION IN ANTIMICROBIAL SUSCEPTIBILITY: 2002*



*Susceptibility rates of urinary *E coli* isolated in hospital laboratories from ambulatory and outpatient men and women 15-50 years of age.

**Average of 1st quarter and 2nd quarter 2002 data.

Source: TSN® Database-USA. Copyright© 2002; Focus Technologies, Inc.[54]

as empiric therapy for infections for which they are not first-choice agents, between 1990 and 1996. In this same period, ciprofloxacin resistance in *E coli* urine isolates increased from 3% to 20% ($P<.00001$).[31] The Netherlands experienced an increase in norfloxacin resistance in uropathogenic *E coli*, from 1.3% in 1989 to 5.8% in 1998, coinciding with close to a doubling of prescriptions for fluoroquinolones between 1990 and 1997.[32] Similar experiences have been described in France, Spain, South America, Korea, the Philippines, and China.[33]

There is evidence that resistance rates in other infections might decrease if antibiotic use were decreased. In Finland, a dramatic increase in macrolide resistance in group A streptococci followed a nearly 3-fold increase in macrolide use. National guidelines to restrict macrolide use were instituted, followed by an approximate 50% reduction in prescriptions for macrolides. Subsequently, a reduction was observed in the macrolide resistance rate in group A streptococci, from 19% in 1993 to 8.6% in 1995.[34]

Multiple-Drug Resistance

Resistance to multiple antimicrobials of different classes is being described increasingly and further complicates therapy. Multidrug-resistant (MDR) isolates are defined as those resistant to 3 or more antimicrobials. In one study, of 38,835 *E coli* isolates tested against the 5 antimicrobials most commonly used in UTI, 7.1% were MDR.[35] Overall resistance rates are shown in Table 4.

A recent large, nationwide study found that ciprofloxacin-resistant bacteria exhibited resistance not only to fluoroquinolones but also to broad-spectrum antimicrobials of other classes, leading authors to conclude that more judicious use of fluoroquinolones is necessary.

Studies have indicated that MDR strains are likely to be resistant to ß-lactams (penicillins and cephalosporins) as well as to TMP/SMX.[35,36] Pathogens resistant to one ß-lactam frequently exhibit cross-resistance to others. Resistance to quinolones as a class has been slow to appear, but some *E coli* express mutated target genes. Strains resistant to ciprofloxacin usually exhibit resistance to other quinolones. A recent large, nationwide study found that ciprofloxacin-resistant bacteria exhibited resistance not only to fluoroquinolones but also to broad-spectrum antimicrobials of other classes, leading authors to conclude that more judicious use of fluoroquinolones is necessary.[37]

Infection with a resistant pathogen leads to poorer clinical and bacteriologic outcomes if an inappropriate antimicrobial is used.

Impact of Resistance on Clinical Management

Antibiotic resistance leads to poorer UTI treatment outcomes. In one study, 12% of women randomly assigned to receive TMP/SMX had uropathogens resistant to the drug. The bacteriologic cure rate in this subset was 50%, compared with 86% for the entire treatment group.[38] Another study reported a clinical cure rate of 60% and a bacterial eradication rate of 50% in women with TMP/SMX-resistant isolates versus more than 90% for women with susceptible isolates.[39] A study involving more than 400 women with UTIs given TMP/SMX reported clinical cure in 88% of those infected with susceptible organisms and in only 54% infected with resistant strains.[40] The clinical failure rates with resistant pathogens in these studies are much higher than the 5% clinical failure rate expected in the treatment of AUC.[41]

Risk factors for infection with uropathogens resistant to TMP/SMX are usually those associated with complicated UTI, including concomitant diabetes, recent hospitalization, and nursing home residence. Also significant are current use of any antibiotic and current or recent use of TMP/SMX. In one study, the strongest risk factor for TMP/SMX-resistant *E coli* infection was use of TMP/SMX at any time during the preceding 3 months.[42] Additional potential risk factors may include travel to areas with high rates of TMP/SMX resistance and exposure to strains of pathogens colonizing children in daycare or household members with recent antibiotic exposure.[26] These potential risk factors require further study.

TABLE 4

ANTIMICROBIAL SUSCEPTIBILITY OF 123,691 *E COLI* URINARY TRACT ISOLATES

Drug	Total No. of Isolates Tested	% Susceptible	% Intermediate	% Resistant
Ampicillin	122,519	60.1	0.8	39.1
TMP/SMX	123,691	81.4	–	18.6
Cephalothin	49,667	70.4	14.0	15.6
Ciprofloxacin	107,342	96.2	0.1	3.7
Nitrofurantoin	105,595	98.1	0.9	1.0

Adapted with permission from Sahm DF, et al. *Antimicrob Agent Chemother*. 2001;45:1403.

Infection with a resistant pathogen leads to poorer clinical and bacteriologic outcomes if an inappropriate antimicrobial is used.[41] Women whose therapy fails because of resistant isolates will require retreatment, leading to further antimicrobial exposure.

Impact of Empiric Use

TMP/SMX and the fluoroquinolones are used to treat a wide range of significant infections in addition to UTI. TMP/SMX indications include acute otitis media, acute exacerbation of chronic bronchitis, and *Pneumocystis carinii* pneumonia; those for ciprofloxacin include lower respiratory infections, skin and skin-structure infections, bone and joint infections, acute sinusitis, and chronic bacterial prostatitis.[43] Both of these drugs are widely used off-label as treatment or prophylaxis for a variety of infections. The increased demand for ciprofloxacin in the fall of 2001, following several cases of anthrax in the United States, is the most notorious example of widespread off-label use.

The increasing resistance to TMP/SMX and ciprofloxacin refocuses attention on drugs such as nitrofurantoin and fosfomycin, with indications limited to treatment of community-acquired UTIs. Nitrofurantoin has been in use for almost 50 years, yet resistance among *E coli* remains very low, although resistance among less common uropathogens, such as *P mirabilis* and *K pneumoniae*, is considerably higher. The drug is not used as a growth promoter in animal husbandry, and, since it is not structurally related to other antimicrobials, even in the rare cases where resistance does emerge, cross-resistance with drugs used to treat more serious infections is not likely.[44]

TREATMENT STRATEGIES FOR AUC

Development of a treatment strategy requires consideration of all relevant diagnostic information including complicating factors, the potential for drug-resistant organisms, local resistance prevalence, patient factors such as previous treatment failures or antibiotic exposure, safety, and cost (Figure 3).

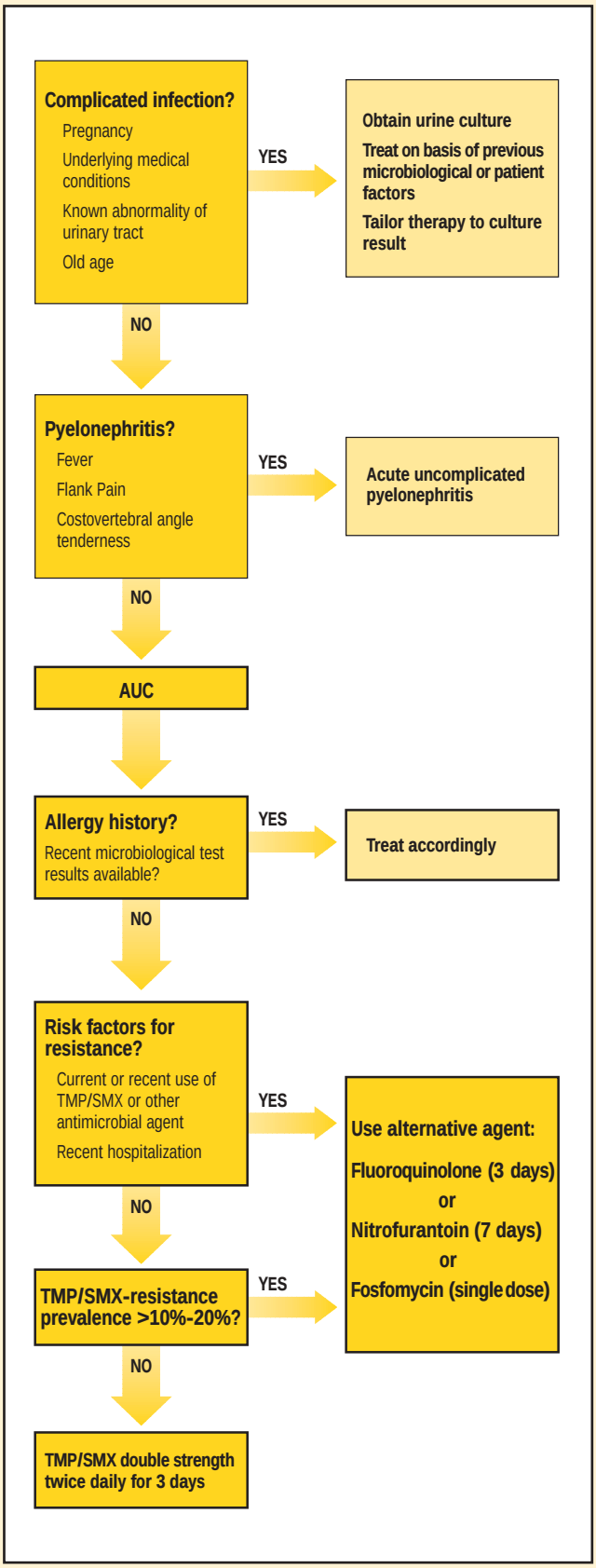
When a diagnosis of AUC is made, drug allergy, recent urine culture results, and the patient's risk for a resistant organism must be considered in antimicrobial selection. Results of previous urine cultures may be helpful, since many women with RUTIs are reinfected with the same organism. Recent antibiotic use, particularly TMP/SMX within the previous 6 months, increases the likelihood of resistance to this drug, and an alternative agent should be considered.[45]

The FDA has stated that local susceptibility patterns should be used in the selection of empiric therapy.

The Infectious Diseases Society of America suggests a 3-day regimen of TMP/SMX for the treatment of AUC, with the proviso that in areas where the prevalence of resistant pathogens is 10% to 20% or higher, alternatives should be considered.[29] The FDA has stated that local susceptibility patterns should be used in the selection of empiric therapy.[28]

FIGURE 3

STRATEGY FOR MANAGEMENT OF UNCOMPLICATED COMMUNITY-ACQUIRED UTIs IN WOMEN



Adapted with permission from Gupta K, et al. *Ann Intern Med*. 2001;135:41-50.

Antimicrobial Agents Commonly Used in Treating AUC

Commonly used antimicrobial agents for AUC are summarized in Table 5.[46-56]

TMP/SMX and TMP

These agents are considered first-line treatment for AUC, although increasing resistance may limit continued use. TMP/SMX is active against most uropathogens, including *E coli*, *S saprophyticus*, *Klebsiella*, *Enterobacter* spp, and *Proteus* spp, but not *Enterococcus*. The most common adverse effects are allergic skin reactions and GI effects. Fewer adverse effects are seen with TMP alone than with TMP/SMX.[57] TMP alone should be used for patients with allergies to sulfa medications.

Fluoroquinolones

There are 7 fluoroquinolones with FDA indications for UTI: Ciprofloxacin, gatifloxacin, levofloxacin, and norfloxacin are used commonly, whereas enoxacin, lomefloxacin, and ofloxacin are used rarely. The fluoroquinolones attain high urinary concentrations, more than 100 times peak plasma levels, making them effective in treating pyelonephritis and complicated UTIs. The most widely used fluoroquinolone in the United States is ciprofloxacin. Fluoroquinolones attain the highest bacteriologic cure rates among the alternatives to TMP/SMX and are active against nearly all gram-negative aerobes and most community-acquired gram-positive pathogens (with the exception of *Enterococcus*). However, routine use of these currently highly effective drugs for empiric therapy may promote further resistance, reducing their effectiveness in more

TABLE 5

COMMONLY USED ANTIMICROBIAL AGENTS FOR ACUTE UNCOMPLICATED CYSTITIS

Drug	Regimen	Clinical Response/ Resolution*	Bacteriologic Response*	Mechanism of Action (MOA)**	Resistance Trends Among *E coli*
TMP/SMX	160 mg TMP/ 800 mg SMX BID X 3 d	90%[46]	94%-96%[46]	TMP blocks tetrahydrofolic acid production; SMX inhibits bacterial synthesis of dihydrofolic acid	↑↑
Nitrofurantoin monohydrate/macrocrystals	100 mg BID X 7 d	89%-94%[47]	78%-79%[47]	Inhibits protein synthesis, aerobic energy metabolism, DNA/RNA synthesis, and cell wall synthesis	–
Nitrofurantoin macrocrystals	50 mg QID X 7 d	90%-92[47]	72%-76%[47]	Inhibits protein synthesis, aerobic energy metabolism, DNA/RNA synthesis, and cell wall synthesis	–
Fosfomycin tromethamine	3-g sachet (SDT)	80%[48,49]	70%-78%[48,49]	Inactivates enzyme enolpyruvul transferase; Interferes with DNA gyrase	↑
Ciprofloxacin	100 mg BID X 3 d	87%-95%[50,51]	91%-97%[50,51]	Interferes with DNA gyrase	↑
	250 mg BID X 3 d	93%-94%[51,52]	90%[51,52]		
	250 mg BID X 7 d	92%-94%[50,52]	97%[50,52]		
	500 mg QD X 3 d	95%[53]	94%[53]		
Levofloxacin	250 mg QD X 3 d	98%[54]	96%[54]	Inhibits topoisomerase IV and DNA gyrase	?†
Gatifloxacin	200 mg QD X 3 d	95%[55]	93%[55]	Inhibits topoisomerase IV and DNA gyrase	?†
	400 mg SDT	90%[56]	95%[56]		

*Responses measured varied per study from 1 to 14 days posttherapy.
**MOA based on drug package inserts.
†Trends not established.
SDT = single-dose therapy

complicated or serious infections. Resistance to the fluoroquinolones arises through mutation in the enzymes DNA gyrase or topoisomerase. Alterations in the pathogen's target cells may confer cross-resistance to other fluoroquinolones, reducing the utility of this entire class of drugs. Systemic ciprofloxacin, regardless of the route of administration, results in low drug levels in nasal secretions and saliva. Respiratory pathogens such as *S pneumoniae* are exposed to low doses of the antimicrobials, which may facilitate acquisition of resistance through mutation.[3] Fluoroquinolones as a class have been associated with a variety of adverse effects, including tendonitis and arthropathies.[58]

Fosfomycin

Fosfomycin tromethamine was recently approved in the United States for treatment of AUC. It is active against gram-negative rods, including the majority of the Enterobacteriaceae. Gram-positive bacteria are less sensitive to fosfomycin. The mechanism of action is through inhibition of cell wall synthesis. The bioavailability of fosfomycin is high, and a single 3-g dose achieves therapeutic urinary concentrations for 1 to 3 days.[33] Side effects include diarrhea, vaginitis, and rhinitis, which occur in less than 1% of patients.[57] Fosfomycin is not recommended for long-term use because of the rapid emergence of resistance.[4] A trial comparing single-dose fosfomycin with a 5-day course of TMP reported bacteriologic eradication rates of 83% in both arms.[59] Fosfomycin is relatively free of side effects, although diarrhea is reported frequently.[33] It is a fairly new drug, so it does not have a long safety record with widespread clinical experience.

The multiple sites of action of nitrofurantoin may partially explain the continued low levels of resistance among *E coli*.

Nitrofurantoin

Nitrofurantoin has been used longer for AUC than any other currently available antimicrobial. The microcrystalline formulation has a high incidence of GI side effects, but the macrocrystalline preparation is much better tolerated. The slow-release formulation allows twice-daily dosing. Nitrofurantoin is metabolized by bacterial nitroreductases, forming several reactive metabolites that inhibit bacterial ribosomal proteins at multiple synthetic levels and disrupt bacterial protein synthesis.[57] The multiple sites of action of nitrofurantoin may partially explain the continued low levels of resistance among *E coli*.[33] Nitrofurantoin is highly active against the most common uropathogens, *E coli* and *S saprophyticus*, and has some activity against several other uropathogens including *Klebsiella*. It is not effective for *Proteus* or *Pseudomonas*. Nitrofurantoin is a urospecific drug, reaching high urine concentrations, but does not achieve effective systemic antimicrobial levels. The urinary tract specificity of nitrofurantoin results in minimal effects on host vaginal and fecal flora, so yeast infections or diarrhea are less common with nitrofurantoin than with other antibiotics. Because nitrofurantoin does not achieve therapeutic levels in the renal parenchyma, it should not be used for treatment of renal infection.[57] Acute or chronic pulmonary reactions and hepatitis occur rarely and resolve with withdrawal of the drug.[57]

Approaches to Prevention of AUC

Prevention is preferable to intervention; however, long-term antibiotic prophylaxis, with the risk of side effects and antimicrobial resistance must be balanced with a cure accomplished with a short course of one of several safe and effective drugs. Patients who use diaphragms and, particularly, spermicide should be counseled regarding the risks of using these forms of contraception and encouraged to consider alternate methods.

Although drinking cranberry juice need not be discouraged, patients should be aware that evidence for benefit remains inconclusive and that large volumes of the juice can add substantially to their daily caloric and sugar intake.

Cranberry Juice

Cranberry juice is a popular nonpharmacologic approach to prevention in the United States and elsewhere. Cranberries and other berries of the *Vaccinium* species contain condensed tannins that appear to act against P-fimbriated *E coli*, preventing bacterial adhesion to cellular surfaces. A 3-armed Finnish study compared cranberry juice with a lactobacillus drink or placebo to prevent infection in 150 women. Women using cranberry juice had 20% fewer RUTIs than did the placebo group. The placebo and lactobacillus groups had similar rates of infection (40% and 39%, respectively).[60] Although drinking cranberry juice need not be discouraged, patients should be aware that evidence for benefit remains inconclusive and that large volumes of the juice can add substantially to their daily caloric and sugar intake.

Probiotics

Probiotics attempt to replenish the normal vaginal flora with lactobacilli to recreate an environment that prevents colonization by potential pathogens. Advocates of this approach claim that selection of probiotics on a scientific basis has great potential to prevent urogenital pathogen adhesion and reduce the incidence of bladder and vaginal infections.[61] Clinical evidence to support a benefit is not convincing, and this method is not recommended until appropriate clinical studies which document efficacy are available.

Topical Estrogen

A promising approach for postmenopausal women is the use of topical intravaginal estrogen. Postmenopausal women experience changes in the vaginal mucosa that favor colonization by pathogens: The vaginal pH increases, lactobacilli disappear from the vaginal flora, and the vagina is colonized by Enterobacteriaceae. In a controlled study with 93 women with very frequent recurrent infection, intravaginal estrogen cream significantly lowered the rate of UTIs to 0.5 per patient year versus 5.9 with placebo ($P<.001$). In women who used topical estrogen, vaginal pH decreased, the rate of colonization with lactobacilli increased, and that of colonization with Enterobacteriaceae decreased.[62] Systemic estrogen therapy has not been shown to decrease the frequency of urinary infection.

Immunization

Trials of vaginal mucosal immunization using suppositories containing killed uropathogens are under way. A small study found no significant differences in the number of UTIs experienced by treatment and control groups and a nonsignificant trend in favor of treatment with regard to preventing reinfection. Further development to increase the immunogenicity of vaginal suppositories is continuing.[63]

Antimicrobial Use in Prevention

For women who experience RUTIs, a preventive option is long-term treatment with low-dose antimicrobials. Many agents, including TMP/SMX, cephalosporins, nitrofurantoin, and the fluoroquinolones, have been shown to be highly effective in preventing UTI recurrence. Although resistance has not been a problem in most studies,[64] antimicrobials with current low resistance rates and which are not likely to develop resistance are preferred. A case series of 200 women who received long-term prophylaxis with nitrofurantoin reported this treatment was effective and safe.[33] Nitrofurantoin, TMP, and TMP/SMX have been shown to be equally effective. If AUC recurs rapidly after discontinuing prophylaxis, it may be resumed.

Women with RUTIs can readily recognize symptoms, make accurate self-diagnoses, and initiate treatment under the guidance of a clinician, appreciably reducing the time between onset and resolution of symptoms and, potentially, lowering overall costs.

Self-diagnosis and patient-initiated treatment may not, strictly speaking, be strategies for prevention; nevertheless, they decrease the impact of AUCs for many women.[45] Women with RUTIs can readily recognize symptoms, make accurate self-diagnoses, and initiate treatment under the guidance of a clinician, appreciably reducing the time between onset and resolution of symptoms and, potentially, lowering overall costs.[45,65]

Managing AUC in the Environment of Managed Care

The primary focus of managed care is to control costs without adversely affecting clinical outcomes. Calculation of the cost-benefit ratio of any treatment is difficult and must consider not only the price of the drug but also the potential costs of inadequate or inappropriate treatment resulting in retreatment, as well as the costs of side effects. In the case of AUC, for instance, if a patient is treated initially with a drug to which the prevailing uropathogen (usually *E coli*) is resistant, the infection may not be eradicated and the patient will need retreatment, possibly with a more expensive drug.

Managed care organizations usually limit their formularies—lists of approved drugs—to 1 or 2 in a class, commonly the least expensive ones. Clinicians are not encouraged to prescribe nonformulary drugs. In one study, however, formulary restriction of drug selection was significantly positively related to increased use of healthcare resources.[66] Another study reported that when specific guidelines limiting treatment choices were strictly enforced, the percentage of patients needing second visits relating to cystitis rose from 12.4% to 16.5%.[67]

Cost calculations related to antibiotic selection are commonly based on drug cost alone, because this information is available and quantifiable. The costs of inappropriate treatment are more elusive. Retreatment usually involves further testing and more drug costs. The primary predictor of the cost-effectiveness of an antibiotic for treating AUC is its efficacy for *E coli*.[68] Managed care organizations need comprehensive, long-range cost-control algorithms that attempt to capture all the costs of a treatment selection for a given problem.

In prescribing drugs to treat AUC, clinicians should select targeted-spectrum antibiotics that are unlikely to encounter or foster resistance. Clinicians need to educate their patients about the risks of antibiotic overuse.

CONCLUSIONS

AUC is a common infection in women, with a lifetime prevalence of 50% to 60%. It results in significant morbidity, and is costly. Treated promptly and appropriately, most cases resolve without complications. However, RUTIs are a significant problem for many women.

Increasing resistance in uropathogens has complicated treatment selection for AUC. Many of the former mainstays of therapy, because of increasing prevalence of resistance, are no longer considered adequate (eg, ß-lactams), or may have lower efficacy than previously (TMP/SMX). There is concern that the rate of resistance to fluoroquinolones is increasing, and that overuse of these antibiotics may impair efficacy for treatment of more serious infections. It is thought that fluoroquinolones should be reserved for the treatment of diseases with graver consequences than AUC, rather than being used widely in empiric therapy for AUC.

Questions about these drugs have refocused attention on nitrofurantoin, an antimicrobial with no clinical indication other than the treatment of lower UTIs and to which *E coli* has developed negligible resistance in nearly half a century of safe and effective use.

Research into strategies to prevent UTIs continues. Some natural remedies may have a role. Intravaginal estrogen is a potential preventive approach for some postmenopausal women. The efficacy of vaccines remains unproven. The only likely effective behavior modification approach, refraining from sexual activity, seems impractical and is not recommended.

Currently, the management of AUC will continue to focus on selection of the antimicrobial that will most reliably and safely resolve symptoms. In prescribing drugs to treat AUC, clinicians should select targeted-spectrum antibiotics that are unlikely to encounter or foster resistance. Clinicians need to educate their patients about the risks of antibiotic overuse.[27,28]

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MANAGING ACUTE UNCOMPLICATED CYSTITIS IN WOMEN IN THE ERA OF ANTIBIOTIC RESISTANCE

POSTTEST

Instructions: To receive CME or CE credit, kindly complete the posttest and evaluation form. Record your answers on the following page.

1. The primary difference between uncomplicated and complicated UTIs is
   a. Uncomplicated UTIs occur much more frequently than complicated UTIs.
   b. Complicated UTIs occur in individuals with abnormalities of the genitourinary tract.
   c. Complicated UTIs carry increased risk for therapy failure.
   d. The antimicrobials used to treat uncomplicated UTIs are ineffective in treating complicated UTIs.

2. Host factors that have been proven to increase the incidence of UTIs include
   a. Postcoitus voiding habits
   b. Methods of menstrual protection
   c. Recent antibiotic use
   d. Fabric composition of underwear

3. Issues that should be considered about antibiotic resistance in the empiric treatment of AUC are
   a. Does antibiotic resistance affect treatment outcomes?
   b. Does antibiotic resistance increase the likelihood of recurrence?
   c. Might the use of antibiotics to treat AUC impair their effectiveness in treating other diseases?
   d. All of the above

4. How does the increased frequency of resistant uropathogens affect treatment decisions?
   a. Resistance to many ß-lactams is in the neighborhood of 30%, limiting effectiveness for empiric therapy.
   b. Resistance to TMP/SMX is approaching the 20% level in many parts of the United States; alternatives may need to be considered.
   c. *E coli* resistance to nitrofurantoin has remained below 1%.
   d. All of the above

5. The strongest risk factor for predicting resistance to TMP/SMX is
   a. Diabetes
   b. Current use of any antibiotic
   c. Hospitalization
   d. Recent use of TMP/SMX

6. The drug that has been used longest without escalating resistance rates is
   a. TMP/SMX
   b. Ciprofloxacin
   c. Nitrofurantoin
   d. Ampicillin

7. Two drugs that are considered safe for use by pregnant women are
   a. Ciprofloxacin and TMP/SMX
   b. Nitrofurantoin and fosfomycin
   c. Ciprofloxacin and nitrofurantoin
   d. TMP/SMX and fosfomycin

8. Nonpharmacologic approaches to prevention of uncomplicated UTIs are
   a. Very promising and may soon supplant antimicrobial therapy
   b. Entirely without scientific basis
   c. In some cases actively harmful
   d. Possibly beneficial and worth trying if the physician is sure they will do no harm

9. The emphasis on restricted drug formularies by managed care organizations may lead to
   a. More consistent treatment from practice to practice.
   b. Reduction of initial cost of treatment, but increase in cost of retreatment.
   c. An increased use of healthcare resources.
   d. All of the above

10. In selecting an antimicrobial for empiric use in AUC, the most important criterion is
    a. Broad spectrum of activity against all urinary pathogens
    b. Maximum efficacy against *E coli*
    c. Rapid onset of action
    d. Cost

For additional continuing medical education opportunities related to this subject, visit The Office on Women's Health of the U.S. Department of Health and Human Services website at: www.4woman.gov/healthpro/contedu

MANAGING ACUTE UNCOMPLICATED CYSTITIS IN WOMEN IN THE ERA OF ANTIBIOTIC RESISTANCE

Course No. EN0302 **For Primary Care Physicians, Obstetrician/Gynecologists, Urologists, Nurse Practitioners, and Healthcare Professionals Who Treat Patients With Acute Cystitis**

CME Credit Information

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the University of Washington School of Medicine and IMED Communications. The University of Washington School of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

The University of Washington School of Medicine designates this educational activity for a maximum of 1.5 category 1 credits toward the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the activity.

Verification of Hours

I certify that I spent ____ hours in this CME activity as indicated by my signature below.

_____

Signature

To apply for category 1 credit, you must:

- Complete the posttest and evaluation form
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EVALUATION FORM

We would appreciate your answers to the following questions in order to help us plan for future activities of this type.

1. How would you rate: (please ✔)

	Excellent	Good	Fair	Poor
a. Value of the topic	❑	❑	❑	❑
b. Relevance to your practice	❑	❑	❑	❑
c. Organization of newsletter	❑	❑	❑	❑
d. Publication length	❑	❑	❑	❑
e. Quality of information	❑	❑	❑	❑

2. Were the goals and objectives clearly stated and achieved? ❑ Yes ❑ No

3. Will reading this newsletter change the way in which you manage patients? ❑ Yes ❑ No

   Please be as specific as possible: _____

4. How did you hear about this program?

   ___ Direct mail ___ Medscape link
   ___ Announcement card ___ Colleague
   ___ OWH/DHHS website ___ Other _____

5. In your opinion, was the information in this newsletter biased toward any commercial product or service? ❑ Yes ❑ No

   If yes, please comment: _____

6. Do you believe such materials, supported by educational grants from industry, are: 10 very appropriate/useful, 0 not appropriate/useful? _____

7. Additional comments and/or suggested topics for future CME activities:

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IMED Communications
Dept. 130
518 Route 513
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